

Answer 1:

Bibliographic Information

Attenuation of the glucocorticoid response during Ad5IL-12 adenovirus vector treatment enhances natural killer cell-mediated killing of MHC class I-negative LNCaP prostate tumors. Raja Gabaglia Claudia; Diaz de Durana Yaiza; Graham Frank L; Gauldie Jack; Sercarz Eli E; Braciak Todd A Division of Immune Regulation, Torrey Pines Institute for Molecular Studies, 3550 General Atomics Court, San Diego, CA 92121, USA Cancer research (2007), 67(5), 2290-7. Journal code: 2984705R. ISSN:0008-5472. (EVALUATION STUDIES); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.) written in English. PubMed ID 17332360 AN 2007132668 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Tumor cells can evolve to evade immune responses by down-modulating surface MHC class I expression and become refractory to T cell-directed immunotherapy. We employed a strategy to bypass this escape mechanism using a recombinant adenovirus vector expressing interleukin-12 (Ad5IL-12) to target natural killer (NK) cell-mediated killing of human prostate tumors in NOD.scid mice. Fluorescence-activated cell sorting analysis revealed that LNCaP tumor cells bear negligible levels of MHC class I molecules; yet, they express MICA/B molecules, ligands for the NKG2D receptors found on NK cells. Transduction of LNCaP cells with the Ad5IL-12 vector prevented tumor formation in NOD.scid mice, indicating that NK cells alone can conduct tumor immunosurveillance and mediate protection. Intratumor injection of the Ad5IL-12 vector to established LNCaP tumors in NOD.scid mice resulted in a significant delay of tumor growth mediated by NK cell killing activity. The dependency of NK cells in this protective response was shown by the complete loss of Ad5IL-12 therapeutic efficacy on LNCaP tumors established in NOD.Cg-Rag1(tm1Mom)Prf1(tm1Sdz) congenic mice, which are devoid of NK cell activity. More pronounced attenuation of tumor growth and enhanced NK killing activity was observed when pharmacologic adrenalectomy with mitotane was done in combination with Ad5IL-12 vector treatment. The Ad5IL-12 vector treatment also induced killing of MICA/B-negative MHC class I-positive PC3 tumors formed in NOD.scid mice. Together, these results indicate that a targeted NK cell response could provide a generic approach for cancer immunotherapy, and that enhancing the NK cell response via control of cortisol levels may provide an additional therapeutic avenue in cancer.